REMARKS

Claims 1-11, 48-65, and 72-134 are pending. Claims 12-47 and 66-71 are cancelled without prejudice or disclaimer. Claims 95-134 are newly entered. At least some of these claims include language in claims withdrawn by the Examiner, but are newly entered to clarify that the claims depend from claim 7. Since these claims depend from claim 7 and further limit claim 7, they read on the elected invention and should also be examined. Accordingly, at least claims 7, 48-65, 72, 73, and 88-134 should be subjected to examination.

The Examiner asserted that the Applicants' previous response was an election without traverse since it failed to point out errors in the restriction requirement. However, in that response, the Applicants stated:

> Certain withdrawn claims are presently amended to depend from claim 7 directly or indirectly. The applicants respectfully request that the examiner rejoin these amended claims and claims dependent therefrom.

Since dependent claims necessarily include the limitations of the parent claim, they are drawn to the same elected invention. If the Examiner finds that restriction is appropriate, the Applicants respectfully request that a formal statement be made of record. See Geneva Pharmaceuticals, Inc. v. Glaxosmithkline Plc, 349 F.3d 1373, 2003 WL 22748633 (Fed. Cir. 2003).

Obviousness Rejection of claim 7

The Examiner rejected claim 7 as obvious over Shultz (WO 90/05785) in view of Wagner (U.S. 6,406,921). Claim 7 relates to a method that includes: providing a substrate that comprises a plurality of addresses, each address comprising (i) a nucleic acid encoding a hybrid amino acid sequence comprising a test amino acid sequence and an affinity tag, and (ii) a binding agent that recognizes the affinity tag; and contacting each address of the plurality with a translation effector to thereby translate the hybrid amino acid sequence.

Thus, the claim requires a substrate that has a plurality of addresses. Each address of which includes a nucleic acid that encodes a hybrid amino acid sequence.

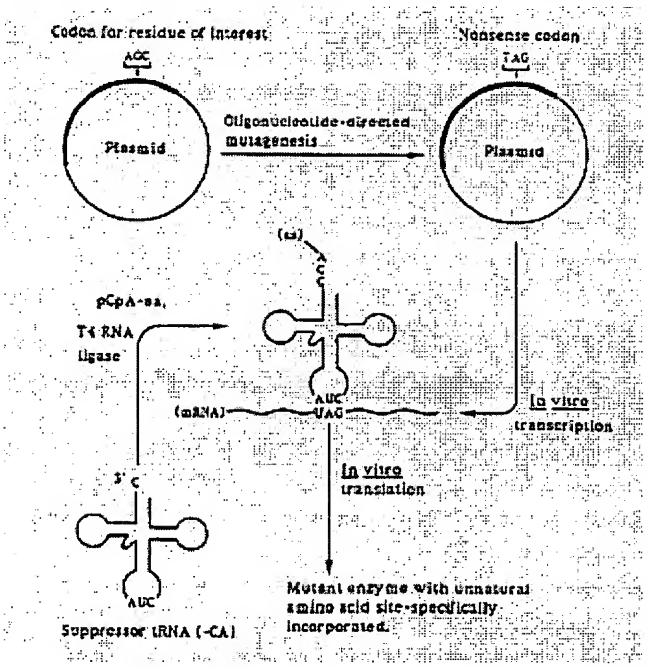
On page 3 of the most recent action, the Examiner alleged that:

Schultz teaches a method comprising providing a substrate that comprises address, each address comprising (I) a nucleic acid encoding a hybrid amino acid sequence comprising a test amino acid sequence and (ii) a binding agent;

contacting each address with a translation effector to thereby translate the hybrid amino acid sequence; and

maintaining the substrate under conditions permissive for the hybrid amino acid sequence to bind the binding agent. (Abstract, Page 13, lines 5-26, page 20, lines 3-11, page 26, lines 3-36, Figure 1, Claim 1-8, and EXPERIMENTAL Section.

However, as described below, Schultz does not describe a substrate that comprises a substrate that comprises a plurality of addresses in which each address comprises a nucleic acid. The principle invention in Schultz was a method of *in vitro* translation that enabled the incorporation of unnatural amino acids at the site of a particular nonsense codon (such as an amber codon) in an engineered gene. See, for example, FIG. 1:



The portions of Schultz cited by the Examiner discuss aspects of *in vitro* translation, but never teach a substrate that comprises a plurality of addresses, much less one in which each address comprises a nucleic acid. The Examiner cites (i) The Abstract, (ii) page 13, lines 5-26, (iii) page 20, lines 3-11, (iv) page 26, lines 3-36, (v) FIG. 1, (vi) claim 1-8, and (vii) The "Experimental Section."

(i) The Abstract states:

> Novel methods are provided for producing proteins, containing unnatural amino acids at specific sites. The methods can utilize modified aminoacyl tRNA's capable of polymerizing a desired unnatural amino acid at unique codons within an mRNA sequence.

Thus, the Abstract does not mention a substrate that includes a plurality of addresses.

(ii) Page 13, lines 5-26 describe *in vitro* translation, and in particular "obtaining or synthesizing an aminoacyl tRNA analogue":

> One aspect of the invention relates to the production of modified tRNA molecules and their use in producing desired proteins as follows:
> a) preparing a nucleic acid sequence capable of being translated into a desired polypeptide, the nucleic acid sequence including at least one codon which will be dedicated to a desired preselected amino acid substitution within the polypeptide;
> b) obtaining or synthesizing an aminoacyl tRNA analogue which will recognize the dedicated codon and function as an adaptor molecule to direct the polymerization of the amino acid substitution into the polypeptide;;
> c) combining the nucleic acid sequence with a protein translation system containing the aminoacyl tRNA analogue, whereby the translation system will function to normally translate the nucleic acid message, except that the aminoacyl tRNA analogue will direct the incorporation of the amino acid substitution for the otherwise naturally occurring corresponding natural amino acid; and
> d) allowing the translation system to function so the sequence will be translated and the system will substitute at the direction of the selected codon the corresponding predetermined amino acid analogue into the resultant protein.

The above-quoted passage also does not mention a substrate that includes a plurality of addresses.

(iii) Page 20, lines 3-11, discusses details of the translation reaction:

> The nascent polypeptide chain is the incompleted polypeptide chain resulting from the translation of the mRNA which is 5' proximate to the current codon. The current codon "directs" the specificity of the next amino acid analogue which is to be polymerized in the nascent chain. In the normal elongation process, the nascent polypeptide chain is polymerized onto the aminoacyl moiety attached to the tRNA which recognizes the codon adjacent to the A site of the ribosome.

(iv) Page 26, lines 3-36 describes an enzymatic reaction for synthesizing an aminoacyl nucleotide to produce a tRNA (which is used in Schultz's *in vitro* translation):

> An alternative method for the synthesis of an unusual aminoacyl tRNA is to synthesize an aminoacyl nucleotide, and then to ligate this moiety onto the appropriate tRNA(-Z) molecule. This method is generally applicable for virtually any aminoacyl tRNA molecule, including attaching normal amino acids, though much less efficient than the synthetase reactions. The only restraints are that the unusual amino acid not interfere with the acylation or deprotection steps and that it not interfere with the ligation step. If so, there is

likely to be alternative chemistry to synthesize the adapter molecule.

The general scheme is to attach the unusual amino acid onto anoligonucleotide and then to ligate together the nucleotide portions, preferably with T4 RNA ligase. A dinucleotide is preferred because it minimizes interference in the chemistry linking the amino acid to the nucleotides and provides a higher efficiency of ligation than a single nucleotide or AppA analogue. Normally the 3' terminal nucleotides on a tRNA are 5'-pCpCpA-3', so the dinucleotide of choice is 5'pCpA-3'. It would likely be possible to use other nucleotides (either di- or oligo) such as deoxy-C-ribo-A (i.e., pdCpA) or an entire deoxy-RNA (i.e., DNA) with a 3' terminal ribo-A. After attachment of the unusual amino acid to the nucleotides, preferably using a dinucleotide, the tRNA(-Z) is ligated to the aminoacyl-multi-nucleotide (aa-MNM) to generate the final aminoacyl tRNA analogue.

The ligation step is performed by chemistry or by enzymatic means, the enzyme may be any which has ligation activity on single stranded RNA molecules. The dinucleotide is a sufficiently long substrate for the T4 RNA ligase used in the examples, other enzymes might require a longer or shorter substrate. It will also be observed that the deprotection reactions might, in some cases, be performed after the ligation step.

Note that the term "substrate" in the context of the above paragraph differs from the usage of the term "substrate" in the context of the Applicants' claim 7. The claimed method refers to a substrate that comprises a plurality of addresses (such as an array) rather than an individual chemical compound (such as a dinucleotide) that is recognized by an enzyme.

(v) FIG. 1 (reproduced above) is described at page 6, lines 28-30, as "a schematic representation of the method for introducing unnatural amino acids site specifically into proteins." The figure does not illustrate a substrate that includes a plurality of addresses.

(vi) Schultz's claims 1-8 and (vii) "Experimental Section" (pages 34-46) describe a method of *in vitro* translation (i.e., in a test tube) and do not disclose a substrate . . . Clearly, nothing in Schultz describes a substrate that comprises a plurality of addresses wherein each address of the plurality includes a nucleic acid that encodes a hybrid amino acid sequence.

Furthermore, Wagner fails to teach or suggest a substrate that comprises a plurality of addresses wherein each address of the plurality includes a nucleic acid that encodes a hybrid amino acid sequence. Wagner relates to arrays of proteins. The addresses of Wagner's array do not include a nucleic acid that encodes a hybrid amino acid sequence, as required by the method of claim 7. Moreover, the use of proteins rather than nucleic acids that might encode such proteins teaches away from the use of a substrate that comprises a plurality of addresses wherein each address of the plurality includes a nucleic acid that encodes a hybrid amino acid sequence.

Since neither Schultz, nor Wagner, nor the combination of Schultz and Wagner teaches or suggests a substrate that comprises a plurality of addresses wherein each address of the plurality includes a nucleic acid that encodes a hybrid amino acid sequence, as required by the method of claim 7, the obviousness rejection of claim 7 should be withdrawn.

Rejection of claims 48-65, 72, 73, and 88-95

The rejections of claims 48-65, 72, 73, and 88-95 all rely on the Examiner's reading of Schultz that the Applicants traverse above. Accordingly, the Applicants request that the rejections of these claims be reconsidered at least for the reasons given above.

The Applicants do not concede any positions of the Examiner that are not expressly addressed above, nor do the applicants concede that there are not other good reasons for patentability of the presented claims or other claims. The cancellations and amendments in the claims are made without prejudice or disclaimer.

Enclosed is a $55 check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: 15 March 2004

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